Solid State Stability

GPEN 2006
The University of Kansas

Polymorphism

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Seminar overview

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- **Literature**
- **Definition**
- **Thermodynamics**
- **Importance in pharmaceuticals**
- **Methods for study**
- **Thermal techniques and calorimetry**
- **Microscopy**
- **Vibrational spectroscopy**
- **Questions**

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Important literature

- Wells JI, ed., Pharmaceutical preformulation, Ellis Horwood, Chichester (1988)
- Giron D, Thermal analysis and calorimetric methods in the characterisation of polymorphs and solvates, Thermochim. Acta, 248, 1-59 (1995)
- Brittain HG, ed., Physical characterization of pharmaceutical solids, Marcel Dekker, NY (1995)
- Brittain HG, ed., Polymorphism in pharmaceutical solids, Marcel Dekker, NY (1999)
- Byrn SR, Pfeiffer R, Stowell JG, Solid state chemistry of drugs, 2nd edn., SSCI Inc., West Lafayette (1999)
- Bernstein J, ed., Polymorphism in molecular crystals, Oxford Science Publications, Oxford (2002)
- Hilfiker R, ed., Polymorphism in the pharmaceutical industry, Wiley-VCH, Weinheim (2005)

Polymorphism definition

- The existence of multiple crystalline structures containing a single chemically defined [molecular] species
- Crystalline nature requires an infinitely repeating [periodic] 3D structure
- Differences between polymorphic solids are abolished on melting or dissolution with solvents
- Highest melting form usually designated Form I or Form A – but this convention is not always followed

Polymorphism types

- **There are two ways in which different crystal structures can arise**
- **Arrangement polymorphism**
  - Rigid molecules with the same conformation packed in different ways
    - > Acetaminophen orthorhombic and monoclinic forms
- **Conformational polymorphism**
  - Flexible molecules with different conformations packed in different ways
    - > Spiperone forms I and II

Polymorphism types

Arrangement polymorphism

Acetaminophen – same conformation

System	**Orthorhombic**	**Monoclinic**
Space group	**Pbca**	**$P2_1/n$**
Unit cell dimensions	**a = 17.17**	**a = 7.09**
	b = 11.78	**b = 9.23**
	c = 7.21	**c = 11.62**
	α = 90.00	**α = 90.00**
	β = 90.00	**β = 97.82**
	γ = 90.00	**γ = 90.00**
Volume	**V = 1458.1 Å^3**	**V = 753.9 Å^3**
Molecules in cell	**Z = 8**	**Z = 4**
Density	**1.377 g/cm^3**	**1.332 g/cm^3**

From Grant, Theory and origin of polymorphism, *in* Brittain, Polymorphism in pharmaceutical solids, Marcel Dekker (1999) Ch. 1

Polymorphism types

Conformational polymorphism

Spiperone – different conformations

System	Monoclinic (I)	Monoclinic (II)
Space group	$P2_1/a$	$P2_1/c$
Unit cell dimensions	a = 12.72	a = 18.57
	b = 7.51	b = 6.07
	c = 21.91	c = 20.68
	α = 90.00	α = 90.00
	β = 95.08	β = 118.69
	γ = 90.00	γ = 90.00
Volume	V = 2085.1 Å^3	V = 2045.7 Å^3
Molecules in cell	Z = 4	Z = 4
Density	1.260 g/cm^3	1.284 g/cm^3

From Grant, Theory and origin of polymorphism, *in* Brittain, Polymorphism in pharmaceutical solids, Marcel Dekker (1999) Ch. 1

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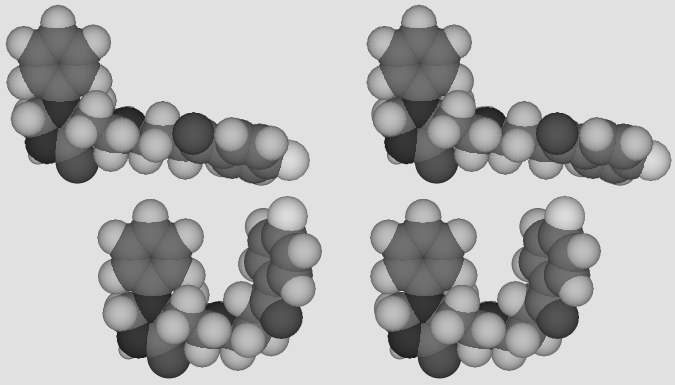
Polymorphism types

Conformational polymorphism

Spiperone – different conformations



Form I conformation

Form II conformation

Polymorphism definition

- **Polymorphs differ from**
  - Pseudomorphs – these crystalline structures also contain solvent molecules, so are not chemically identical to the anhydrous form(s)
    - > More degrees of freedom (Gibbs' phase rule)
  - Amorphous solids – these solids have random local organization, but have no 3D periodicity
- **Very useful to think of polymorphic pairs**
  - e.g., A-B; A-B, B-C, etc
- **Enantiotropic *vs* monotropic polymorph pairs**
  - Fundamental differences in their thermodynamic properties

Thermodynamics and polymorphism

A pure solid can be envisaged in terms of its free energy (G), enthalpy (H) and entropy (S) as a function of temperature

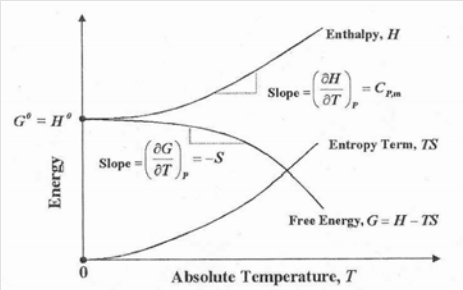
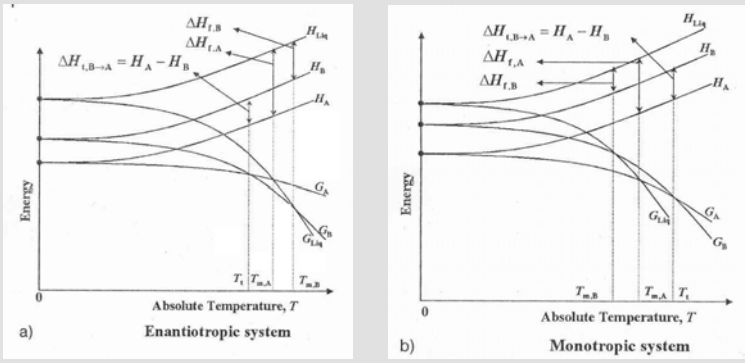


Fig. 2.1 Energy–temperature diagram of a crystalline solid under constant pressure. (Adapted from [1]).

From Lohani and Grant, Thermodynamics of polymorphs, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 2

Thermodynamics and polymorphism

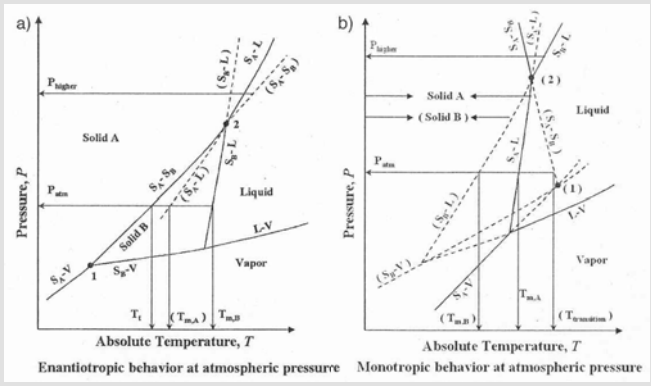
- **When a pair of polymorphs are related, the polymorph with the lowest free energy is the most stable**



From Lohani and Grant, Thermodynamics of polymorphs, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 2

Thermodynamics and polymorphism

- **Pressure dependency of polymorphic pair behavior**



From Lohani and Grant, Thermodynamics of polymorphs, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 2

Thermodynamics and polymorphism

- **Thermodynamic relationships**
  - Gibbs' equation: $\Delta G = \Delta H - T\Delta S$
  - For $\Delta G = 0$; $\Delta S = \Delta H/T$
  - Allows calculation of entropy change for fusion from DSC enthalpy of fusion data
  - To ensure that $\Delta G = 0$, the system must be at equilibrium
  - This requires a temperature change so slow that there are no temperature gradients in the system – typically 1 K/min

From Lohani and Grant, Thermodynamics of polymorphs, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 2

Thermodynamics and polymorphism

- **Predictions for polymorph stability**
  - Heat of transition rule
  - Enthalpy of fusion rule
  - Entropy of fusion rule
  - Heat capacity rule
  - Density rule
  - Infra-red rule
  - Solubility rule

From Lohani and Grant, Thermodynamics of polymorphs, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 2

Thermodynamics and polymorphism

- **Heat of transition rule**
  - An endothermic enthalpy of transition is seen for enantiotropic pairs
  - An exothermic enthalpy of transition is seen for monotropic pairs
- **Enthalpy of fusion rule**
  - When the higher melting polymorph of a pair also has the higher enthalpy of fusion, they are monotropically related

From Grant, Theory and origin of polymorphism, *in* Brittain, Polymorphism in pharmaceutical solids, Marcel Dekker (1999) Ch. 1

Thermodynamics and polymorphism

- **Entropy of fusion (ΔS_f) rule**
  - When one polymorph has both the higher melting point and the higher entropy change for fusion, they are enantiotropically related
  - The ΔS_f value is relatively easy to measure
- **Heat capacity (Cp) rule**
  - When one polymorph has both the higher melting point and the higher heat capacity (at fixed T), they are enantiotropically related
  - The Cp value is more difficult to measure

From Lohani and Grant, Thermodynamics of polymorphs, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 2

Thermodynamics and polymorphism

- **Density rule (for non-hydrogen bonded solids only)**
  - Density of the higher melting enantiotropic form is less than for the lower melting form
- **Infra-red rule (for hydrogen bonded crystals)**
  - The higher entropy form has the higher bond stretching frequency

From Grant, Theory and origin of polymorphism, *in* Brittain, Polymorphism in pharmaceutical solids, Marcel Dekker (1999) Ch. 1

Thermodynamics and polymorphism

- **Solubility rule**
  - Where the higher melting form has the higher solubility at temperatures above the transition temperature, the polymorphs are enantiotropic
  - The solubility of the higher melting member of a pair of monotropes is always lower than for the lower melting member

From Grant, Theory and origin of polymorphism, *in* Brittain, Polymorphism in pharmaceutical solids, Marcel Dekker (1999) Ch. 1

Thermodynamics and polymorphism

- **Summary**
  - Metastable forms can always convert to the stable form in the solid state
  - Enantiotropic pairs can always be interconverted in the solid state by changing temperature.
    > The transition temperature is real
  - Monotropic pairs can never be interconverted in the solid state by merely changing the temperature – the liquid or solution state is needed.
    > The transition temperature is hypothetical
  - Interconversion may also occur due to pressure changes (see P *vs* T diagram)

Pharmaceutical importance

- **Any pharmaceutical property of a solid will be influenced by its polymorphic form**
  - Packing aspects (molar volume, density, refractive index, hygroscopicity)
  - Thermodynamic (melting temperature, internal energy, heat capacity, enthalpy, entropy, free energy, solubility, thermodynamic activity, vapor pressure)
  - Kinetic factors (sublimation rate, dissolution rate, solid state reaction kinetics, chemical stability, shelf-life)
  - Surface (interfacial tension, surface free energy, habit)
  - Spectroscopic (UV, IR, Raman, microwave, NMR)
  - Mechanical (compressibility, hardness)

Adapted from Grant, Theory and origin of polymorphism, *in* Brittain, Polymorphism in pharmaceutical solids, Marcel Dekker (1999) Ch. 1

Early examples

Early examples of polymorphic drugs:

- **Phenylbutazone**
  - Five forms with variable solubility
- **Chloramphenicol palmitate**
  - The palmitate ester was synthesized to give a poorly water soluble, tasteless form
  - Three polymorphs of the ester, A, B and C
  - Classic work by Aguiar et al showed that Form C reverted very rapidly to Form B, which reverted very slowly to Form A. Form B had 100% oral bioavailability, while Form A was 0% bioavailable

Early examples

More early examples of polymorphic drugs:

- **Barbiturates – more than 60% of all barbiturates shown to display multiple polymorphic (or pseudomorphic) forms**
  - Some had up to 12 forms
- **Multiple hydrogen-bonding patterns**
  - Each barbiturate molecule usually donates two H-bonds, but has six H-bond acceptor sites
- **Steroids and sulfonamides**
  - Polymorphism also common

Later examples

More examples of polymorphic drugs:

- **Spironolactone – some forms known to have compromised oral bioavailability**
  - Eight forms including pseudomorphs
- **Furosemide**
  - Two forms with significantly differing aqueous solubility and dissolution rate
  - Oral bioavailability compromised

Recent example

An embarassing recent case:

- **Ritonavir – after release on the market, a previously unknown polymorph (Form II) was found as crystals in the final product**
  - An example of conformational polymorphism
  - The newer, more stable form took about 2 years to appear after market release
  - The more stable polymorph was 5-fold less soluble than Form I
  - A new formulation was required

Excipients

Examples of polymorphic excipients:

- **Classic example is that of cocoa butter used to make suppositories – 6 forms**
  - It has been long known that suppositories made from cocoa butter can convert to a higher melting form, giving lower bioavailability
- **Giron lists >20 excipients that display polymorphism, including**
  - Lactose (anhydrous; also monohydrate)
  - Aspartame (anhydrous; hydrate forms)
  - Magnesium stearate (can affect lubrication of tablets)
  - Triglycerides (α, β, β' forms)

Methods for study of polymorphism

All of the phenomena mentioned could be used

- **The more techniques used, the better the results, especially when different probes are used**
- **Focus on thermal methods**
- **Definition of thermal methodology**
  - ICTA definition: A group of techniques in which a physical property of a substance and/or its reaction products is measured as a function of temperature whilst the substance is subjected to a controlled temperature program.
- **Excludes isothermal calorimetry – discussed separately**

Thermal techniques

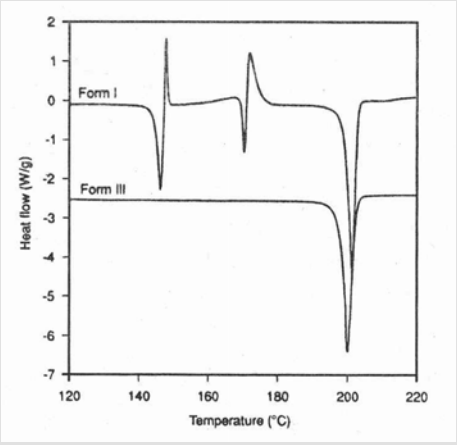
Wide range of techniques

- **Differential thermal analysis (older literature)**
- **Differential scanning calorimetry (DSC)**
- **Modulated Temperature DSC (MT-DSC)**
- **High Speed DSC (HS-DSC)**
- **Thermogravimetric analysis (TGA)**
- **High resolution TGA**
- **Evolved gas analysis (EGA)**
- **Hot Stage Microscopy (HSM)**
- **Thermomechanical analysis (TMA)**
- **Microthermal analysis**
- **Isothermal Calorimetry**

Differential Scanning Calorimetry

Measures the heat flux as a function of temperature

- Premafloxacin Forms I and III
- Exothermic transitions suggest monotropic pairs I, II and II, III
- Note change to the usual convention of naming the highest m.p. as Form I

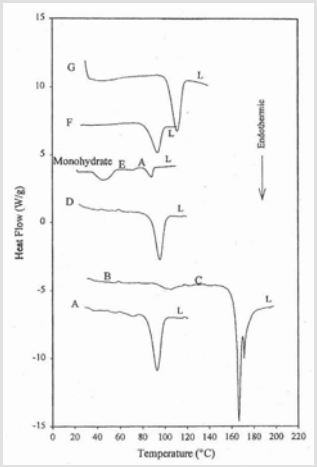


From Schinzer et al, J. Pharm. Sci., 86, 1426-31 (1997)

DSC

Further example showing enantiotropic pairs

- Neotame Forms A to G
- Forms A, D, F and G gave single melt endotherms
- Forms A, E and B, C are enantiotropically related pairs

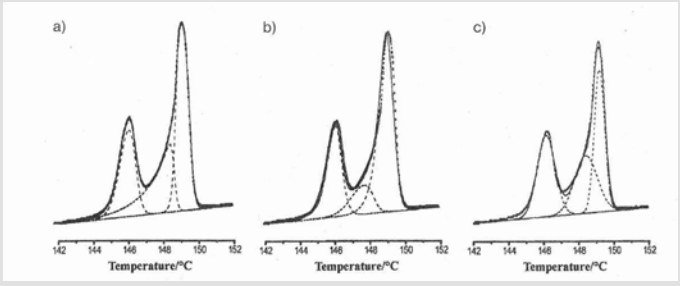


From Craig, Characterization of polymorphic systems…, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 3

DSC

Quantify mixtures – extension of purity analysis

- Terfenadine polymorphs
- Deconvolution of a multi-event signal into the individual components – use of different fitting algorithms

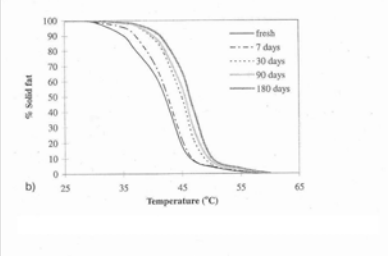


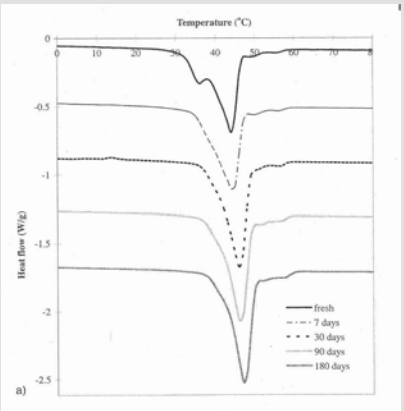
From Leitao et al, Study of polymorphism from DSC melting curves; Polymorphs of terfenadine, J. Therm. Anal. Calorimetry, 2002, 68, 397-412

DSC

Can be used to monitor time-dependent changes

- Gelucire solid fat content





From Craig, Characterization of polymorphic systems…, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 3

Modulated Temperature DSC

Method for determining heat capacity as function of temperature

- Periodic temperature variation superimposed on normal temperature program
- Used to study transitions of frusemide polymorphs
- The frusemide transition was dominated by reversible heat flux (2nd order process)

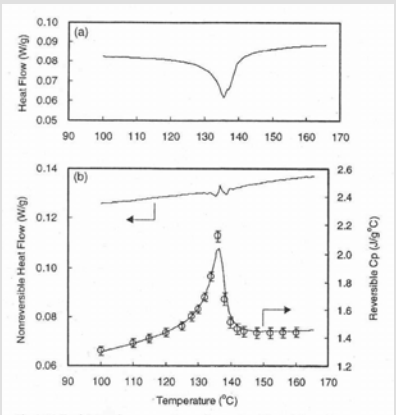


Fig. 3.16 Total (a) and non-reversing and reversing (b) heat flows for frusemide. Open circles represent quasi-isothermal measurements

From Craig, Characterization of polymorphic systems…, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 3

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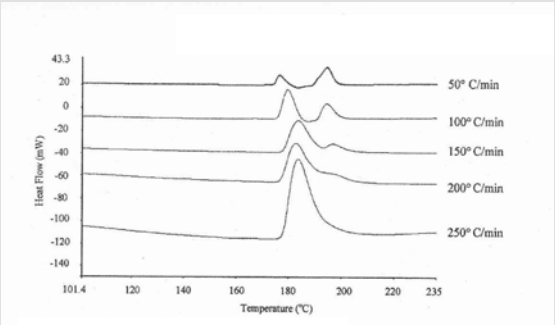
High Speed DSC

Some metastable polymorphs are so poorly stable that they interconvert before melting

– Carbamazepine low melting form



From Craig, Characterization of polymorphic systems…, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 3

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DSC in combination

Polymorphs shown by DSC-Raman spectroscopy

sn-1,3-distearoyl-2-oleylglycerol showed five polymorphs with different m.p.s and variations in Raman stretching frequencies

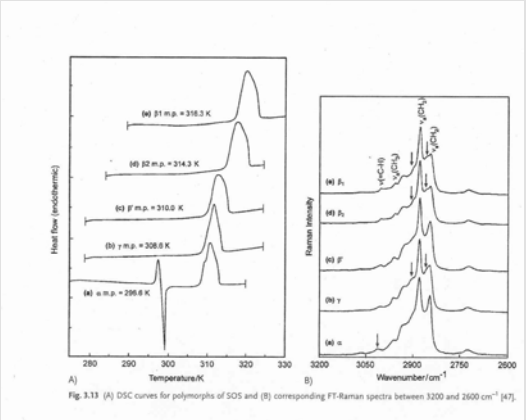


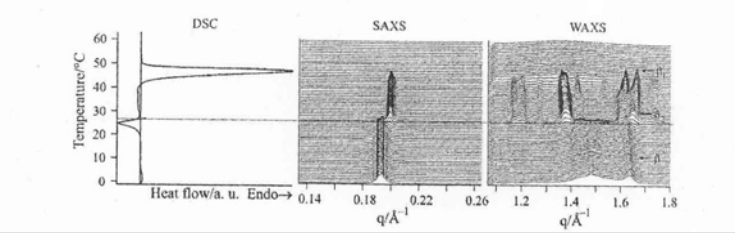
Fig. 3.13 (A) DSC curves for polymorphs of SOS and (B) corresponding FT-Raman spectra between 3200 and 2600 cm^{-1} [47].

From Craig, Characterization of polymorphic systems…, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 3

DSC in combination

Transitions confirmed by DSC coupled synchrotron radiation scattering (SAXS and WAXS)

- Trilaurin-cholesterol system (96:4) shows β' to β_2 transition (completed at 28° C; confirmed by SAXS)
- WAXS also shows β_2 to β_1 transition before the main melting endotherm at 45° C



From Craig, Characterization of polymorphic systems…, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 3

TGA

Measures change in mass *vs* temperature

- **Main use in pharmaceutical study of solids is to characterize volatiles**
  - adsorbed water (non-stoichiometric surface moisture)
    - > often lost in temperature range 70-110° C
  - crystal water (stoichiometric; bound water)
    - > usually lost above 100° C; rarely held above 160° C
  - other adsorbed solvents
  - other crystal solvates
  - TGA mass loss is commonly correlated with thermal events monitored by DSC
    - > moisture loss normally shown by broad endotherm

High Resolution TGA

Measures change in mass *vs* temperature

- **Mass loss detection is used to trigger an automatic reduction in heating rate while the mass loss is occurring**
  - Rapid heating between mass loss events minimizes thermal decomposition of samples
  - Slow temperature increase during the mass loss event increases the resolution of events that otherwise may overlap

Evolved Gas Analysis

Usually coupled to TGA

- **identifies desorbed volatiles by gas phase infra red spectroscopy, mass spectrometry, thermal conductivity, etc.**
  - has the potential to characterize polymorphs by measurement of solid vapor pressure
  - could be used to assess stability of carboxylate polymorphs by measuring decarboxylation
  - often used in characterization of the plastics used in pharmaceutical packaging

Isothermal calorimetry

Measures enthalpy change as a result of a defined physical change, e.g., solution formation

- often useful when DSC cannot be used to measure ΔH_f
- Auranofin polymorphs (Lindenbaum *et al*, IJP, 26, 123)

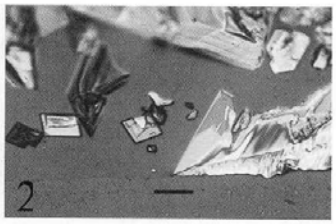
Enthalpy change	95% EtOH	DMF
ΔH_{sol} (form A)	12.42 kcal/mol	5.57 kcal/mol
ΔH_{sol} (form B)	9.52 kcal/mol	2.72 kcal/mol
$\Delta(\Delta H_{sol})$(form A → form B)	2.90 kcal/mol	2.85 kcal/mol
= ΔH_{trans})(form A → form B)	DSC gave ~3.20 kcal/mol	

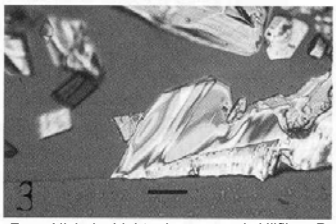
Hot Stage Microscopy

Allows visual observation of polymorphs during temperature program

- high magnification possible (up to 1250x)
- use of polarized light illumination and crossed polarizer analysis
- anisotropy shown by birefringence patterns
- measurement of angles between crystal axes
  - > Changes occur on polymorphic change
- vapor from heated pseudopolymorph can be detected by heating under layer of silicone oil

Hot Stage Microscopy

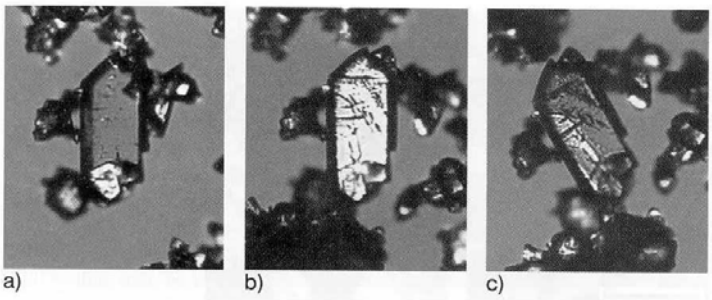




Changed birefringency displays polymorphism – the β form converts to the α form of KNO_3

From Nichols, Light microscopy, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 7

Microscopy



Solid state change from acetaminophen Form II to Form I shown by change in extinction. After rotation of the stage, extinction of polarized light is restored.

From Nichols, Light microscopy, *in* Hilfiker, Polymorphism, Wiley-VCH (2005) Ch. 7

Thermomechanical Analysis

Two major types

- **Compression**
  - Allows measurement of the compressibility of polymorphic materials, e.g., drugs and excipients for tabletting
- **Stress**
  - Mainly applied to plastics for packaging, IV sets, etc.

Vibrational spectroscopy

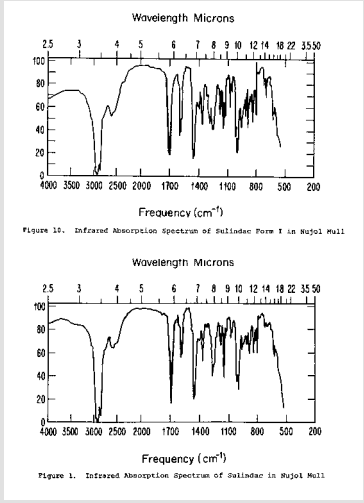
Two major types

- **Infra-red spectroscopy**
- **Raman spectroscopy**
  - Both techniques rely on polymorphism differences in their intermolecular interactions influencing the vibrational energies of their intramolecular bonds
  - Especially applies to bonds involving H-bonded atoms

IR spectroscopy

Example: Sulindac

- **Two forms**
- **IR spectral differences supported by XRPD and by thermal analysis**

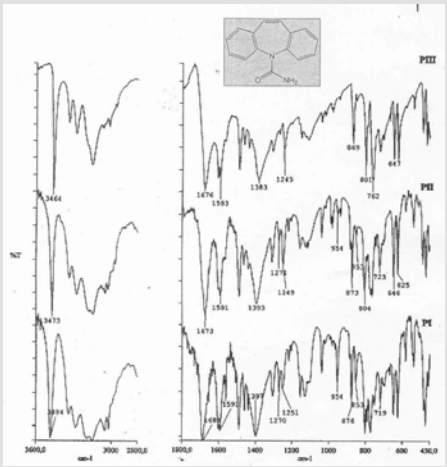


From Analytical Profiles of Drug Substances, vol 13, 586-590

IR spectroscopy

Example: Carbamazepine

- **Three forms**
- **IR spectral differences are quite clear**

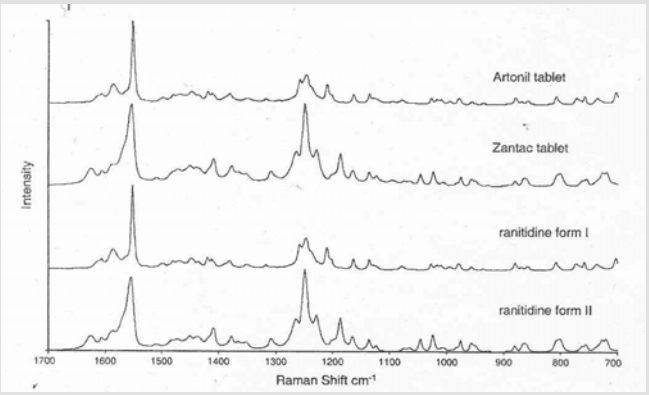


From Chalmers and Dent *in* Hilfiker, Polymorphism, Fig 5.14

Raman spectroscopy

Example: Ranitidine

- **FT-Raman clearly shows marketed tablets contain different polymorphs**



From Chalmers and Dent *in* Hilfiker, Polymorphism, Fig 5.24

Questions

Thank you for your attention!

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Now introducing…

Professor Thomas Rades